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# Letter to the Editor: Second Cancers in Patients With Ewing's Sarcoma

Nicholson et al. report a significant excess of second malignancies among 29 5-year survivors of Ewing's sarcoma, based on the occurrence of three osteosarcomas and one cervical carcinoma in situ [1]. All osteosarcomas occurred in previously irradiated sites, although alkylating agents had also been administered to two patients [2]. Earlier studies have estimated a 30- to 80-fold risk of all second cancers following Ewing's sarcoma, based on small numbers of cases [3-6]. These surveys taken together have included 11 osteosarcomas and eight other malignancies, including one acute nonlymphocytic leukemia (ANLL) and two leukemias in which the cell type was not specified [1,3–6].

In order to further examine the risk of all second malignancies following Ewing's sarcoma, we analyzed data reported to the Connecticut Tumor Registry (1935–1989) and other population-based registries participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (1973–1989). These cancer registries, which comprise approximately 10% of the U.S. population, collect data on initial treatment, although information on specific drugs or type of radiotherapy is not available. Among 595 patients with Ewing's sarcoma who survived for at least 2 months, 13 second cancers developed, compared with 1.53 expected (observed/expected ratio, 8.5; 95% confidence interval 4.5–14.5) (Table I). All malignancies were histologically confirmed. ANLL developed in one patient initially treated with chemotherapy alone, and in another subject who had received both chemotherapy and radiotherapy; intervals between diagnoses of Ewing's sarcoma and subsequent ANLL were 33 and 29 months, respectively. All other second malignancies, with the exception of the testicular cancer, occurred in 5-year survivors. Cancers of the lung, colon, uterine corpus, and endocrine system (malignant thymoma) occurred in patients initially treated with radiotherapy only. The remaining malignant neoplasms occurred in subjects given combined modality therapy. One of the osteosarcomas and three soft tissue sarcomas (including two malignant fibrous histiocytomas) were located within the irradiated field. The second osteosarcoma occurred at a site apart from the initial Ewing's sarcoma.

**TABLE I. Second Cancers Following Ewing's Sarcoma†**

| Site | Observed No. | O/E | 95% CI |
|---|---|---|---|
| All second cancers | 13 | 8.5* | 4.5–14.5 |
| Colon | 1 | 9.1 | 0.2–50.6 |
| Lung | 1 | 12.5 | 0.3–69.6 |
| Uterine corpus | 1 | 16.7 | 0.4–92.8 |
| Testis | 1 | 16.7 | 0.4–92.8 |
| Endocrine | 1 | 200.0* | 5.1–1,114 |
| Bone | 2 | 100.0* | 12.0–361 |
| Connective tissue | 3 | 100.0* | 20.4–292 |
| Hodgkin's disease | 1 | 12.5 | 0.3–69.6 |
| ANLL | 2 | 66.7* | 8.0–241 |

†Includes 595 2-month survivors with 2,333 person-years' of follow-up. Abbreviations: ANLL = acute nonlymphocytic leukemia; CI = confidence interval; O/E = observed/expected ratio of second cancers. *$P < .05$.



These results from population-based cancer registries indicate that patients with Ewing's sarcoma are at a significantly increased risk of all second cancers, including ANLL. Patients in whom ANLL developed were diagnosed with Ewing's sarcoma in the mid-1980s, when treatment likely included cyclophosphamide, doxorubicin, vincristine, and dactinomycin. Of these, only cyclophosphamide is currently considered a leukemogen, perhaps a weak one [7]. In several earlier reports, four patients with Ewing's sarcoma who later developed ANLL had been treated with radiotherapy, cyclophosphamide, doxorubicin, and vincristine, with three patients also receiving other drugs, including carmustine in one subject [6,8–10]. A possible inherent relationship between Ewing's sarcoma and ANLL has also been suggested [10]. Our results underscore the need for additional research to clarify the role of treatment, as well as other factors, in the subsequent development of ANLL, sarcomas, and possibly other malignancies in patients with Ewings sarcoma.

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